New claims 61 and 62 are supported by original claims 34 and 35. Support for the other new claims is discussed below.

Claims 10 and 25 were objected to by the Office as being dependent on non-elected claims. *See* Office Action, Paper No. 15, page 2, lines 14-17. Applicants have amended claims 10 and 25 to be independent claims, which no longer depend on any other claims. Therefore, Applicants respectfully request that the objection be withdrawn.

35 U.S.C. § 112, second paragraph

Claims 10-22 and 25-38 were rejected under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter of the invention under a number of different grounds.

First, the Office rejected claims 10, 16, and 25-38 because the term "capable of" was found to be indefinite. *See* Office Action, Paper No. 15, page 3, lines 6-9. Applicants have amended these claims to remove the term "capable of," thus obviating the rejection on these grounds.

Next, claim 10 was rejected as being vague and indefinite because of the term "generating a signal amplification." *See* Office Action, Paper No. 15, page 3, lines 10-12. Applicants have amended this term to "amplifying a signal," thus obviating the rejection on these grounds.

The Office also found the term "leads to" in claim 12 to be vague and indefinite. *See* Office Action, Paper No. 15, page 3, lines 13-14. Applicants have amended this claim to recite the term "results in" instead of "leads to," as the Office suggested. Applicants request that the rejection on these grounds be withdrawn.

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Claims 14 and 27 were rejected because the term "whose activity is restored" was found to be vague and indefinite. *See* Office Action, Paper No. 15, page 3, lines 15-17. Applicants have amended this term to "wherein the activity of the enzyme is restored." Because the term is now definite, Applicants request that the rejection be withdrawn.

Claims 15 and 32 were rejected because the term "ligand" was both characterized in the Markush group and listed as a member of the Markush group. *See* Office Action, Paper No. 15, page 3, lines 18-19. Applicants have deleted the term "ligand" from the Markush group of claims 15 and 32 and respectfully request that the rejection be withdrawn.

Claims 18, 19, 34, and 35 were rejected because the phrase "signaling molecule corresponds to the synthesis of cAMP" or "signaling molecule corresponds to the synthesis of cGMP" were found to be vague and indefinite. *See* Office Action, Paper No. 15, page 3, lines 20 through page 4, line 3. Applicants have amended claims 18 and 34 to recite "signaling molecule is a component of the cAMP signaling cascade reaction" and have amended claims 19 and 35 to recite "signaling molecule is a component of the cGMP signaling cascade reaction." These amendments are supported on page 17, lines 26-28 of the specification. Because these phrases are definite, Applicants request that the rejections be withdrawn.

Claims 20 and 36 were rejected for several reasons. First, the syntax of the Markush group was considered to be incorrect. *See* Office Action, Paper No. 15, page 4, lines 4-5. Second, the use of the phrases "such as" and "of the type of" were determined to be indefinite. *See* Office Action, Paper No. 15, page 4, lines 6-8. And

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third, the phrase "the reporter gene expression is selected from the group consisting of" was found to be indefinite when describing a process or a function. *See* Office Action, Paper No. 15, page 4, lines 9-11. Applicants have amended claims 20 and 36 to recite "wherein the reporter gene is a gene with a selectable phenotype." This phrase is definite and Applicants request that the rejection of the claims be withdrawn. In addition, Applicants have added new claims 46-51, which depend on claim 20 and new claims 52-57, which depend on claim 36. These new claims were derived from the elements of original claims 20 and 36 and so do not add new matter.

Claims 21 and 37 were rejected because the Office found the term "mutant molecule" to be vague and indefinite. *See* Office Action, Paper No. 15, page 4, lines 12-14. This term has been deleted and the claims have been amended to recite "wherein the amino acid sequence of the molecule of interest is mutated compared to the amino acids sequence of the wild type molecule." This term is no longer vague, and Applicants request that the rejection to claims 21 and 37 be withdrawn. In addition, Applicants note that the clean version of claim 37 in the Preliminary Amendment submitted on December 28, 2001, included the term "[to 36]" this term should have been deleted from the claim as indicated by the brackets around the expression "to 36".

Claims 22 and 38 were rejected because the Office found the phrase "an *E. coli* strain, or in any bacterial deficient in endogenous adenylate cyclase or any other eukaryotic cell" to be vague and indefinite. *See* Office Action, Paper No. 15, page 4, lines 15-21. Applicants have amended claims 22 and 38 to recite "wherein the selection is performed in a bacterial strain." The selection in a bacterial strain is supported by original claims 22 and 38. New claims 58 and 59, dependent on claims 22 and 38,

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respectively, recite *E. coli* strains and bacterial strains that are deficient in endogenous adenylate cyclase, which are supported on page 8, lines 26-28 of the specification. Applicants have deleted the Markush language objected to by the Office, *see* Office Action, Paper No. 15, page 4, line 21 through page 5, line 3, with the amendments to claims 22 and 38, and the addition of new claims 58 and 59 render the claims definite. Applicants respectfully request that the rejection of claims 22 and 38 be withdrawn.

Claim 25 was rejected as indefinite because the Office found the phrase "generating an amplification" to be vague and indefinite. *See* Office Action, Paper No. 15, page 5, lines 4-7. Applicants have amended this claim to recite "generating an amplified signal," which is definite. Therefore, Applicants respectfully request that the rejection be withdrawn.

Finally, the Office rejected claim 33 as being vague and indefinite because of the term "having stimulated or inhibitory affinity." *See* Office Action, Paper No. 15, page 5, lines 8-10. Applicants have amended this claim to recite "wherein the substance increases or decreases the affinity between the target ligand and the molecule of interest." Because the claim is now definite, Applicants respectfully request that the rejection be withdrawn. In addition, Applicants have added new claim 60 which provides that the substance that increases or decreases the affinity between the target ligand and the molecule of interest is a protein, glycoprotein, or lipoprotein. This claim is derived from original claim 33 and therefore does not add new matter.

All of the amendments to the claims allow them to conform to United States patent practice and English syntax. None of the amendments adds new matter.

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35 U.S.C. § 102(b)

Claims 10-17, 20-22, 25-33, and 36-38 were rejected under 35 U.S.C. § 102(b) as being anticipated by Fields *et al.*, U.S. Patent 5,468,614. *See* Office Action, Paper No. 15, pages 5-6. The Office asserted that Fields *et al.* disclose "generally applicable methods for detecting any detectable function requiring separable domains of an amino acid sequence which can be reconstituted," Office Action, Paper No. 15, page 6, lines 13-14, and that the amino acid sequence might be derived from a number of different proteins including an enzyme.

To anticipate under 35 U.S.C. § 102(b), a prior art reference must recite each and every element of the claimed invention. *See Verdegaal Bros. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Fields *et al.*, though, does not disclose each and every element of the claimed invention.

In particular, Fields *et al.* does not disclose the use of enzyme fragments in a bacterial multi-hybrid signal amplification system. Although the Office asserted that Fields *et al.* discloses the use of any proteins or protein fragments that are capable of interacting, including enzymes or fragments of enzymes, Applicants submit that Fields *et al.* does not recite the use of an enzyme. Fields *et al.* states:

> The functions of GAL4 can be served by any transcriptional activator that has separable domains for DNA binding and for transcriptional activation. Indeed, any protein, even one that is not a transcriptional activator, that has two separable functions can be used to establish a similar genetic system to detect protein-protein interactions.
>
> Accordingly, the method of the present invention can be applied more generally to any detectable function requiring separable domains of an amino acid sequence which can be reconstituted. This general embodiment of the present invention detects interaction between a first test protein and a second test protein.

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col. 7, lines 43-55. This disclosure mentions only transcriptional activators, but does not disclose use of an enzyme in a bacterial multi-hybrid signal amplification system. Without disclosure of an enzyme in Fields et al., the claimed invention is not anticipated by Fields *et al.* Accordingly, Applicants respectfully request that the rejection of the claims be withdrawn.

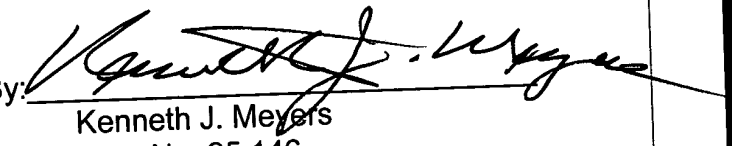
In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 10, 2003

By: 

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Appendix to the Amendment of January 10, 2003

Please amend the claims as follows:

10. (TWICE AMENDED) A method of selecting a molecule of interest [which is capable of binding] that binds to a target ligand, wherein the method comprises:

(1) providing a signal amplification system that comprises a bacterial multi-hybrid system of at least two chimeric polypeptides comprising:

(A) a first chimeric polypeptide comprising a first fragment of an enzyme;

(B) a second chimeric polypeptide comprising a second fragment of an enzyme or a modulating substance capable of activating the enzyme;

wherein the first fragment is fused to a molecule of interest and the second fragment or modulating substance is fused to a target ligand;

(2) contacting the [wherein the interaction between the said] molecule of interest and the [said] target ligand;

(3) amplifying a signal generated by contacting the molecule of interest and the target ligand in (2) with the signal amplification system of (1) [is detected with a signal amplification system as claimed in claim 1, by means of generating a signal amplification]; and,

(4) triggering transcriptional activation;

wherein activity of the enzyme is restored by *in vivo* interaction between the molecule of interest and the target ligand, which generates the amplified signal in (3).

11. (AMENDED) The method of selecting a molecule of interest [according to] as claimed in claim 10, wherein the signal amplification [corresponds to] comprises the production of a signaling molecule.

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12. (AMENDED) The method of selecting a molecule of interest [according to] as claimed in claim 10, wherein the transcriptional activation [leads to] results in expression of a reporter gene [expression].

14. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme and a modulating substance[, whose activity is restored by the interaction between the said molecule of interest and the said target ligand].

15. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the target ligand is selected from the group consisting of protein, peptide, polypeptide, receptor, [ligand,] antigen, antibody, DNA binding protein, glycoprotein, lipoprotein, and recombinant protein.

17. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the interaction between the molecule of interest and the target ligand is detected[,] by [means of] signal amplification [which] that triggers transcriptional activation, and is quantified by measuring the synthesis of [the] a signaling molecule or [the] expression of [the] a reporter gene.

18. (AMENDED) The method of selecting a molecule of interest [according to] as claimed in claim 11, wherein the signaling molecule [corresponds to the synthesis of cAMP] is a component of a cAMP signaling cascade reaction.

19. (AMENDED) The method of selecting a molecule of interest [according to] as claimed in claim 11, wherein the signaling molecule [corresponds to the synthesis of cGMP] is a component of a cGMP signaling cascade reaction.

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20. (AMENDED) The method of selecting a molecule of interest [according to] as claimed in claim 12, wherein the reporter gene [expression is selected from the group consisting of gene coding for nutritional marker such as lactose, maltose; gene conferring resistance to antibiotics such as ampicillin, kanamycin or tetracyclin; gene encoding for toxin; color marker such as fluorescent marker of the type of the Green Fluorescent Protein (GFP); gene encoding for phage receptor proteins or fragment thereof such as phage λ receptor, *lamB* and any other] is a gene [giving] with a selectable phenotype.

21. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein [the] an amino acid sequence of the molecule of interest is [a mutant molecule] mutated compared to [the known] an amino acid sequence of the wild type molecule and said molecule of interest is tested for its [capacity of interacting] ability to interact with the target ligand.

22. (TWICE AMENDED) The method of selecting a molecule of interest as claimed in claim 10, wherein the selection is performed in a bacterial strain[an *E. coli* strain, or in any bacterial strain deficient in endogenous adenylate cyclase or any other eukaryotic cell].

25. (TWICE AMENDED) A method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest wherein the method comprises: [respectively the stimulating or the inhibiting activity is detected with a signal amplification system as claimed in claim 1, by means of generating an amplification and respectively of]

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(1) providing a signal amplification system that comprises a bacterial multi-hybrid system of at least two chimeric polypeptides containing:

(A) a first chimeric polypeptide comprising a first fragment of an enzyme;

(B) a second chimeric polypeptide comprising a second fragment of the enzyme or a modulating substance capable of activating said enzyme;

wherein the first fragment is fused to a molecule of interest and the second fragment or the modulating substance is fused to a target ligand;

(2) contacting the molecule of interest and the target ligand in the presence of the substance;

(3) amplifying a signal generated by contacting the molecule of interest and the target ligand in (2) with the signal amplification system of (1);

(4) triggering or [of] abolishing transcriptional activation, [and]

wherein the activity of the enzyme is restored by *in vivo* interaction between the molecule of interest and the target ligand, which generates the amplified signal in (3); and

(5) comparing said signal amplification [and said triggered or abolished transcriptional activation are compared] with [those] the one obtained from an identical signal amplification system [without any] in the absence of the substance, wherein a difference in the signal amplification in the presence and absence of the substance indicates that the substance stimulates or inhibits the interaction between the target ligand and the molecule of interest.

26. (AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand

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and a molecule of interest [according to] as claimed in claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least two distinct fragments of an enzyme, [whose] wherein the enzymatic activity is restored by the interaction between the [said] molecule of interest and the [said] target ligand.

27. (AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest [according to] as claimed in claim 25, wherein the signal amplification system comprises a bacterial multi-hybrid system of at least a first fragment of an enzyme and a modulating substance[, whose activity is restored by the interaction between the said molecule of interest and the said target ligand].

28. (TWICE AMENDED) The method of screening for a substance [capable of stimulating] that stimulates the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification [corresponds to] comprises the production of a signaling molecule.

29. (TWICE AMENDED) The method of screening for a substance [capable of inhibiting] that inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the signal amplification [corresponding to the production of a signaling molecule] is blocked or partially abolished.

30. (TWICE AMENDED) The method of screening for a substance [capable of stimulating] that stimulates the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the transcriptional activation [leads to a] results in reporter gene expression.

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31. (TWICE AMENDED) The method of screening for a substance [capable of inhibiting] that inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the transcriptional activation [leading to] results in a reporter gene expression which is blocked or partially abolished.

32. (TWICE AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the target ligand is selected from the group consisting of receptor, [ligand,] antigen, antibody, DNA binding protein, glycoprotein and lipoprotein.

34. (TWICE AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 28, wherein the signaling molecule [corresponds to the synthesis of cAMP] is a component of a cAMP signaling cascade reaction.

35. (TWICE AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 28, wherein the signaling molecule [corresponds to the synthesis of cGMP] is a component of a cGMP signaling cascade reaction.

36. (TWICE AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 30, wherein the reporter gene [expression is selected from the group consisting of a gene coding for nutritional marker such as

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lactose, maltose; gene conferring resistance to antibiotics such as ampicillin, kanamycin or tetracyclin; gene encoding for toxin; color marker such as fluorescent marker of the type of the Green Fluorescent Protein (GFP); gene encoding for phage receptor proteins or fragment thereof such as phage λ receptor, *lamB* and any other] is a gene [giving] with a selectable phenotype.

37. (TWICE AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the amino acid sequence of the molecule of interest is [a mutant molecule] mutated compared to the [known] amino acid sequence of the wild type molecule and said molecule of interest is tested for its [capacity of interacting] ability to interact with the target ligand.

38. (TWICE AMENDED) The method of screening for a substance [capable of stimulating or inhibiting] that stimulates or inhibits the interaction between a target ligand and a molecule of interest as claimed in claim 25, wherein the screening is performed in a bacterial strain[an *E. coli* strain, or in any bacterial strain deficient in endogenous adenylate cyclase or any other eukaryotic cell].

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